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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,746	05/23/2007	Andreas Bergmann	2582.012	9538

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EXAMINER	
COUNTS, GARY W	
ART UNIT	PAPER NUMBER
1641	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,746	BERGMANN ET AL.	
	Examiner	Art Unit	
	GARY W. COUNTS	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5-24* is/are pending in the application.

4a) Of the above claim(s) *20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-19 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment filed 08/11/10 is acknowledged and has been entered. Currently, claims 1 and 5-24 are pending. Claims 20-23 are withdrawn as being directed to non-elected inventions. Claims 1, 5-19 and 24 are under examination.

Claim Objections

1. Claim 9 is objected to because of the following informalities: Claim 9, line 2 the recitation "secondantibodies" should be --second antibodies--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. 1, 5-19 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while appearing to be enabling for a method for detecting C-terminal fragments of preproendothelin-1 (SEQ ID NO:1) in sample selected from the group consisting of whole blood, plasma or serum, wherein the sample is collected from a human patient suffering from cardiovascular disease, systemic inflammatory response syndrome (SIRS), and sepsis by contacting the sample with antibodies which specifically bind within amino acids 168-181, 184-203 and 200-212 of preproendothelin-

1, does not reasonably provide enablement for any and all antibodies and any and all sequence positions within amino acids 168-212 of preproendothelin-1 or detection in any inflammatory or cancer condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining undue experimentation are set forth in *In re W*ands USPTQ2d 14000. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are directed to an in vitro method for the determination of the formation of endothelins in a human patient suspected of a disease selected from the group consisting of cardiovascular disease, inflammation, sepsis and cancer wherein the formation of endothelin-1 (SEQ ID NO:2) and big endothelin-1 (SEQ ID NO: 3) is determined by detecting a C-terminal fragment of preproendothelin-1 (SEQ ID NO: 1), the method comprising: obtaining a whole blood, plasma or serum sample from the patient; contacting said sample with first antibodies that specifically bind to a first epitope within amino acids 168-212 of preproendothelin and second antibodies that specifically bind to a second epitope within amino acids 168-212 of preproendothelin,

one of said first and second antibodies being labeled with a detectable marker, wherein the level of a C-terminal fragment detected by said first and second antibodies correlates with the level of formation of endothelin-1 (SEQ ID NO: 2) or big endothelin-1 (SEQ ID NO: 3) in said patient.

The specification fails to teach any and all antibodies bind to any and all sequence combinations of amino acids 168-212 of preproendothelin-1 and also fails to teach that any and all cancers or forms of inflammation are associated with the formation of such endothelins. The specification on page 12, lines 1-8 discloses the peptide fragment determined is a c-terminal fragment to which two antibodies bind which bind to peptides having amino acid sequences which correspond to the positions 168-181 and 200-212 of preproendothelin-1. The specification on pages 22-23 discloses assays wherein antibodies were raised against the positions 136-148, 168-181, 184-203, and 200-212 and utilized in assays with samples from cardiological and sepsis patients. However, the specification clearly teaches that in the assay wherein antibodies directed against amino acids 136-148 were used that it was not possible to obtain measured values raised compared with healthy persons. Thus, it appears that the only working examples which provide for the detection of C-terminal fragments of preproendothelin-1 are directed to antibodies which bind within amino acids 168-181, 184-203, and 200-212 of preproendothelin-1. Further, antibodies which bind to c-terminal fragments of preproendothelin-1 are not well known in the art and as shown by Applicant not all sequences of preproendothelin-1 provide for the detection of the C-terminal fragments in samples from patients suffering cardiological or sepsis conditions. For example, the

specification does not provide examples of epitopes or antibodies to such combinations e.g. as amino acids 168-169, 169-170, 169-179, 170- 205, 170-206, 182-183, 182-212, 183-212, 184-212, 184-203, 184-195, 187-188, 195-212 etc. Also, the specification does not provide guidance or examples of inflammation or cancer and the formation of endothelins in any and all forms of cancer or inflammation. It appears that the specification does not provide a single example of cancer or inflammation as correlated to the instantly recited claims. The specification fails to provide for the use of any and all antibodies to bind to any and all positions of sequences within amino acids 168-212 and provide for the detection of C-terminal fragments of preproendothelin-1 in samples from patients suffering cardiovascular, inflammations, sepsis and cancer. At best the detection C-terminal fragments of preproendothelin-1 (SEQ ID NO:1) can be detected by contacting the sample from the patients with antibodies that specifically bind within amino acids 168-181, 184-203 and 200-212 of preproendothelin-1. Thus such is not seen as sufficient to support the breath of the claims and one skilled in the art cannot practice the claimed invention without undue experimentation, because in order to have a high level of predictability, one skilled in the art would have to know that all antibodies to amino acids 168-212 of preproendothelin-1 would bind to any position and combination within amino acids 168-212 and that these antibodies would detect the C-terminal fragments of preproendothelin-1 in samples from patients suffering from cardiovascular diseases, any and all inflammations, sepsis, and any and all cancers. Thus, one skilled in the art cannot practice the claimed invention without undue experimentation because of the unreasonable spectrum of subjects, diseases many of

which could not conceivably provide for the detection of entothelins and the unreasonable amount of different combination of amino acid sequences contained within amino acids 168-212.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 5-19 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, line 15 the recitation “a C-terminal fragment detected” is vague and indefinite because it is unclear if Applicant if referring to the C-terminal fragment detected in lines 7-8 or if Applicant intends another C-terminal fragment.

Claim 1 is vague and indefinite because it is unclear how the formation of endothelin-1 and big endothelin-1 is determined in whole blood, plasma or serum because the claim is directed to detecting C-terminal fragments ofpreproendothelin-1. In the method recited the antibodies bind to first and second epitopes within amino acids 168-212. However, it is unclear how the level of C-terminal fragment is accomplished with the use of these antibodies and correlated to the level of formation of endothelin-1 or big endothelin-1 because from the instant claims it appears that the antibodies would also bind to preproendothelin-1 (amino acids 1-212) because preproendothelin-1 would also include amino acids 168-212. Therefore, it appears that

both preproendothelin-1 and C-terminal fragments of preproendothelin-1 would be captured. Thus, how would one know that endothelin-1 and big endothelin-1 are formed if the whole preproendothelin-1 (amino acids 1-212) is captured. The instantly recited claims do not make clear if the antibodies are only specific to C-terminal fragments 168-212 or if the antibodies bind to the C-terminal portion of the 1-212 preproendothelin-1 molecule. Page 6 discloses determining not ET or big ET but a comparatively long-lived prepro- or proendothelin partial peptide which does not contain the ET or big ET sequences. Applicant is reminded that limitations from the specification are not read into the claims. See also deficiency found in claim 24.

Claim 6, line 2 the recitation "a C-terminal fragment" is vague and indefinite because it is unclear if Applicant is referring to the C-terminal fragment recited in lines 7-8 of claim 1, the C-terminal fragment recited in line 15 of claim 1 or if Applicant intends another C-terminal fragment.

Claim 24, line 12 the recitation "a C-terminal fragment detected" is vague and indefinite because it is unclear if Applicant if referring to the C-terminal fragment detected in line 4 or if Applicant intends another C-terminal fragment.

Response to Arguments

6. Applicant's arguments filed 08/11/10 have been fully considered but they are not persuasive.

Applicant argues that the disclosure of the identity and structure of a surrogate marker for endothelin-1 and/or big endothelin-1 in the case of amino acids 168-212 of

preproendothelin-1 provides the general knowledge of one of skill in the art would, as a matter of routine, enable her to make and screen the appropriate antibodies for a dual antibody assay for the detection of amino acids.

This argument is not found persuasive because the enablement rejection is not solely based on the production of antibodies and screening of antibodies but also is directed to diseases and conditions such as any type of cancer or any inflammation and correlating levels of C-terminal fragments of preproendothelin-1 to levels of endothelin-1 and big endothelin-1. Also, with respect to the antibodies as stated by Applicant the Applicant has only disclosed three antibodies which have been shown to work in the method (e.g. remarks, page 11, last paragraph). Further, as disclosed by Applicant on pages 22-23 not all sequences of preproendothelin-1 provide for the detection of the C-terminal fragments in samples from patients suffering the conditions as recited. Thus, the predictability of any combination of amino acids 168-212 raises the question is any antibody made to any combination of the references capable of binding to any epitope in amino acids 168-212. Further, the number of combinations for amino acids 168-212 is unreasonable, thus causing undue experimentation.

Conclusion

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GARY W. COUNTS whose telephone number is (571)272-0817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ Gary W. Counts/
Examiner, Art Unit 1641

/Melanie Yu/
Primary Examiner, Art Unit 1641